REMARKS

The Office Action

Claims 33 – 51 have been examined. Claims 33, 49, and 50 stand objected to for having typographical errors. Claims 43, 44, and 49-50 are rejected as being indefinite. Claims 33-38 and 40-51 stand rejected for obviousness over Wyburn-Mason (U.S. Patent No. 4,073,922) in view of ADAP Drugs and the PDR Electronic Library (see Office action for weblinks). Claims 33-51 stand further rejected for obviousness over Wyburn-Mason in view of ADAP Drugs, PDR Electronic Library, and Jensen et al. (U.S. Patent No. 6,545,028; hereafter "Jensen"). Each of these rejections is addressed in turn below.

Objections to the Claims

Claim 33 is objected to for having a typographical error. Claims 42 and 45 have been corrected for spelling errors. Claims 43, 44, 49 and 50 have been amended for clarity. Applicants have corrected these defects by amendment.

Rejections under 35 U.S.C. § 112

Claims 43-44 and 49-50 are rejected under § 112 as being indefinite. According to the Office, "[t]he term 'low' is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." Applicants have addressed this rejection by amending "low dose" to –low dosage–. This term is defined

at page 7, line 17, as meaning "less than 10 mg per day of prednisolone or equivalent, or fluconozole or equivalent. In view of this amendment, this rejection may now be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 33-51 stand rejected for obviousness over Wyburn-Mason in view of ADAP Drugs, the PDR Electronic Library, and Jensen. According to the Office, Wyburn-Mason teaches a method of treating rheumatoid arthritis with clotrimazole and further teaches that corticosteroids have been commonly used in treating rheumatoid arthritis. Moreover, according to the Office,

> [C]ombining agents which are known to be useful to treat rheumatoid arthritis individually into a [single] composition useful for the very same purpose is prima facie obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the very same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining an azole and a steroid flows logically from their having been individually taught in the prior art.

Applicants respectfully traverse this rejection.

The legal standard for obviousness, found in M.P.E.P. 2142, requires some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; a reasonable expectation of success; and a teaching or suggestion of all the claim limitations in the prior art reference (or references when combined). This standard has not been met in the present case.

Wyburn-Mason teaches the administration of clotrimazole for the treatment of rheumatoid arthritis (RA). As acknowledged by the Office, Wyburn-Mason does not, in any way, teach or suggest that the combination of clotrimazole and corticosteroids offer a treatment for RA. In fact, Wyburn-Mason's invention is a *replacement therapy* for corticosteroids since, according to Wyburn-Mason, corticosteroids "bring temporary relief to the arthritic patient but present the danger of side effects and the physician has to balance the potential benefit against the risks" (column 1, lines 47-50). If it is obvious to combine clotrimazole and a corticosteroid, why didn't Wyburn-Mason suggest doing so? Why, in the nearly 30 years since Wyburn-Mason published, has this combination not been used to treat rheumatoid arthritis? (The Office contends that "people suffering from rheumatoid arthritis have been using both treatments separately for example if one treatment fails or the condition is not ameliorated with only one treatment," but the Office fails to cite any evidence supporting this contention).

None of ADAP Drugs, the PDR Electronic Library, and Jensen remedies the deficiency of Wyburn-Mason. ADAP drugs teaches that clotrimazole is sold as 10 mg lozenges, the PDR Electronic Library teaches that hydrocortisone is supplied in 10 mg dosages, and Jensen simply teaches that azoles such as fluconazole are "medicaments for the treatment or alleviation of diseases, disorders or conditions relating to immune dysfunction" (col 3, lines 28-30). None teach or suggest combining an azole and a corticosteroid to treat rheumatoid arthritis.

The only basis put forth to support the rejection of the claims as being obvious is the assertion by the Examiner based on *In re Kerkhoven*, 625 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) that "since it is prima facie obvious to combine two agents each of which is taught in the prior art to be useful for same purpose, in order to form third composition that is to be used for very the same purpose, the idea of combining an azole and a steroid flows logically from their having been individually taught in the prior art."

According to MPEP § 2144, legal precedent can be used as a rationale for supporting a *prima facie* case of obviousness only if the facts in the case are sufficiently similar to those in the application. Applicants submit that the facts of the present case are not sufficiently similar to those of *Kerkhoven* and therefore do not meet this standard.

In *Kerkhoven*, the appellants claim processes for the production of a particulate detergent composition. The process covers methods for mixing the detergent ingredients of one slurry, which is anionic in nature, with the detergent ingredients of another slurry, which is nonionic in nature. Under one of appellants' claimed methods, the slurries are independently dried and the resulting products mixed. Under the other claimed method, the slurries are simultaneously dried and mixed. The Examiner rejected the claims under 35 U.S.C. § 103 on the basis that the claims require no more than the mixing of two conventional spray-dried detergent compositions and concluded that the mere mixing of two compositions each taught for the same purpose, in the absence of a showing of unexpected results, is obvious.

In contrast to *Kerkhoven,* where the Examiner "determined that appellant had not demonstrated any unexpected advantage for the claimed process," Applicants in the present application provide evidence in the specification demonstrating the unexpected effectiveness of combining a corticosteroid and an azole *in vitro*. For example, the specification notes "[k]etoconazole is often administered at 200 mg/day orally and reaches a serum concentration of about 3.2 micrograms, while prednisone is generally administered in amounts between 5-200 mg. We demonstrate that we can achieve a 10-fold increase in the potency of the steroid by combining it, at 5 mg/day, with 100 mg ketoconazole" (page 3, lines 7-15). Combination data presented in Tables 1 to 2 of the specification again shows synergy when an azole and a steroid are used in combination. For example,

> Data from a second experiment (Table 2) confirm and extend the observed synergism between azole and glucocorticoid. Clotrimazole can greatly increase the potency of the steroid diflorasone. As a single agent, diflorasone can suppress TNF-α secretion from P/I stimulated PBMCs by 29% at a single agent concentration of 3.8 nM. This level of TNF-α suppression (28%) can be achieved by only 0.5 nM diflorasone in the presence of 0.250 μM clotrimazole. This represents a potency shift for the diflorasone of 8-fold. In the presence of 2 μM clotrimazole, 65% TNF-α inhibition is achieved by 120 nM diflorasone. Furthermore, this level of activity is not achievable by diflorasone alone (47%), even at very high concentrations that risk serious side effects. The combination of clotrimazole and diflorasone would therefore provide a more effective and safer TNF-α suppressive therapy than steroid treatment alone (page 15, lines 13-14 and page 16 lines 1-11).

One could not have predicted at the time the invention was made that the combination of an azole and a steroid would produce a synergistic effect or that such a combination

would allow a dramatic reduction in the amount of steroid required to achieve the same therapeutic effects.

In sum, while the references cited by the Examiner provides a list of potential therapeutics for rheumatoid arthritis, they do not teach or suggest the unique combination of a steroid with an azole as claimed in claims 33-51, nor do they provide a motivation to combine the references to arrive at this combination. Furthermore, it is not predictable based on the cited references that combining a steroid with an azole would produce a beneficial effect in the treatment of RA as discovered by Applicants in the present invention.

For all of the above reason, Applicants assert that the Examiner has not established a *prima facie* case of obviousness and, in view of the unexpected results provided herein, the rejection of claims 33-51 for obviousness may be withdrawn.

CONCLUSION

Enclosed is a Petition to extend the period for replying to the Office action for one month, to and including March 16, 2006, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 3/13/06

Michael J. Belliveau, Ph.D.
Reg. No. 52,608

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045